

University of California, San Francisco (UCSF) Comprehensive Cancer Center

CLINICAL TRIAL

RATIONALE:

Chemotherapy drugs like 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) work in different ways to cause tumor cells to stop growing or die. Bevacizumab is a monoclonal antibody that may inhibit cancer growth by blocking blood flow to tumors. Adding bevacizumab to combination chemotherapy may be a better way to block tumor growth than giving either type of therapy alone. The FOLFOX plus bevacizumab combination is being studied in patients with neuroendocrine tumors because FOLFOX appears to inhibit the growth of a variety of different tumor types but has not yet been tested in this disease. In addition, neuroendocrine tumors appear to depend on blood vessels for growth suggesting that they may respond to a treatment like bevacizumab. This clinical trial is for patients who have not responded to other treatments to see if the FOLFOX/bevacizumab combination is safe and if it can inhibit the growth of metastatic neuroendocrine tumors.

PURPOSE:

The treatment of advanced neuroendocrine tumors (NET) has been a major challenge for treating physicians. NET encompasses a heterogeneous group of diseases for which standard treatment approaches are lacking, particularly in patients with refractory disease. FOLFOX has not yet been studied in NET, but appears to have activity across a range of tumor types. In addition to the known activity observed with metastatic colorectal cancer, FOLFOX plus bevacizumab combination therapy has been shown to have activity in patients with metastatic colorectal cancer. Additionally, it has been suggested that bevacizumab can be safely combined with FOLFOX chemotherapy in the second-line setting and leads to improved survival compared to chemotherapy alone in patients with metastatic colorectal cancer. NET expresses VEGF and are highly vascular, suggesting that VEGF is a valid therapeutic target in this disease. Given the ability of bevacizumab to enhance the effects of chemotherapy and the broad spectrum of activity of FOLFOX chemotherapy across a range of tumor types, we plan to evaluate the safety and efficacy of FOLFOX plus bevacizumab in patients with progressive, metastatic neuroendocrine tumors.

OFFICIAL TITLE:

A Pilot Study of FOLFOX in Combination with Bevacizumab in Patients with Advanced Neuroendocrine Tumors

OBJECTIVES:

Primary Objectives:

1. To determine the safety of FOLFOX with bevacizumab in patients with advanced neuroendocrine tumors.
2. To determine the objective radiographic response rate of FOLFOX with bevacizumab in patients with advanced neuroendocrine tumors (best overall response after six months of treatment).

Secondary Objectives:

1. To determine overall survival.
2. To determine time to treatment failure.
3. To determine time to progression.
4. To determine biochemical marker response.

OUTLINE:

This is a single center, open-label, phase I/II, study. Patients will be stratified according to tumor type: carcinoid, islet cell, or poorly differentiated neuroendocrine tumor. Patients will receive oxaliplatin 85 mg/m² IV, leucovorin 200 mg/m² IV, and 5-fluorouracil 400 mg/m² IV bolus on day 1 followed by 5-fluorouracil 2400 mg/m² CIV over 46-48 hours on days 1-2. Using a second IV site, bevacizumab 5 mg/kg IV will be administered on day 1. Courses will be repeated every 14 days in the absence of disease progression or unacceptable toxicity up to 26 cycles.

NCI Cancer Clinical Trials Common Toxicity Criteria (Version 3.0) will be formally evaluated every 2 weeks. After every 4 cycles, radiographic studies (CTs) and biochemical markers will be assessed. The primary efficacy endpoint, objective response rate, will be confirmed by the investigator after 12 cycles of therapy (24 weeks).

PROJECTED ACCRUAL:

A total of 39-102 patients will be accrued to this study within 12 months.

ELIGIBILITY:

Inclusion criteria:

Pathologic (histological or cytological) confirmation of neuroendocrine tumor including carcinoid (any site, with or without carcinoid syndrome),

pancreatic islet cell tumor, or poorly differentiated NET (regardless of primary site)

Radiologic or clinical evidence for progressive disease at time of enrollment

Disease that is not amenable to surgery, radiation, or combined modality therapy with curative intent

Progression on prior treatment with taxane- or cisplatin- or carboplatin-based chemotherapy required for patients with poorly differentiated NET (unless contraindicated)

Measurable disease

At least 4 weeks since prior chemotherapy

At least 4 weeks since prior radiotherapy

Prior treatment only allowed if does not affect areas of measurable disease being used for protocol

At least 4 weeks since prior immunotherapy or investigational therapy

Prior chemoembolization and cryotherapy only allowed if does not affect areas of measurable disease being used for protocol

Prior and concomitant use of somatostatin analogs is allowed for symptomatic control and/or control of hormone hypersecretion (provided treatment was initiated > 3 months prior to study entry)

18 years or older

Male or female

ECOG Performance Status 0 or 1

ANC \geq 1500 μ l

Platelets \geq 100,000 μ l

Total Bilirubin < 2 mg/dL

ALT \leq 2.5x upper limit normal (5x ULN if liver metastases)

Creatinine \leq 2 mg/dL

Urinalysis \leq 1+ protein, if \geq 1+, then 24-hour urine collection must show < 500 mg protein

Urine protein: creatinine ratio < 1.0

Blood pressure \leq 150/100 mmHg

History of thromboembolic condition requiring ongoing full-dose anticoagulation allowed if patient on therapeutic anticoagulation with stable dose for >4 weeks prior to enrollment
Female patients of childbearing potential must have negative pregnancy test <7 days before study enrollment and must agree to use a medically effective method of contraception

Life expectancy > 12 weeks

Exclusion Criteria:

Small cell variants, endocrine organ carcinomas or adrenal gland malignancies (including thyroid carcinoma of any histology, merkel cell tumor, and pheochromocytoma/paraganglioma)

Major surgical procedure <28 days prior to Day 0

Anticipated major surgical procedure during the course of the study

Prior oxaliplatin

Prior bevacizumab

Prior treatment with a tyrosine kinase inhibitor or VEGF inhibitor

Concomitant investigational therapy

History of uncontrolled hypertension, myocardial infarction, or angina <24 months prior to registration

History of cerebrovascular event (stroke or TIA)

Clinically significant peripheral vascular disease (Grade II or greater) or New York Heart Association Grade II or greater congestive heart failure

lung tumor in close proximity to a major vessel or with associated cavitation, or history of hemoptysis (bright red blood of >1/2 teaspoon)

History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess <6 months prior to Day 0

History of or evidence for brain or leptomeningeal disease on physical examination or uncontrolled seizures

Known hypersensitivity to any of the study drugs or to compounds of similar chemical or biological composition
Symptomatic peripheral neuropathy > CTC grade 1

Second invasive cancer other than basal cell and squamous cell carcinoma of the skin, or carcinoma in situ of the cervix

Open biopsy or significant traumatic injury <28 days prior to Day 0

Minor surgical procedures, fine needle aspirations, or core biopsies <7 days prior to Day 0

Uncontrolled small bowel or colonic disorders

Severe, concurrent disease, infection, or co-morbidity that in the judgment of the investigator would constitute a hazard for participation in this study (including but not limited to):

- Active infection
- Serious non-healing wound, ulcer, or bone fracture
- Organ allograft
- Psychiatric illness/social situations that would limit compliance with study requirements
- Evidence of bleeding diathesis or coagulopathy (unrelated to therapeutic anticoagulation)

LOCATION AND CONTACT INFORMATION

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